

REVIEW



## Safety of Japanese encephalitis vaccines

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### ABSTRACT

Japanese encephalitis (JE) is an endemic disease dominantly in the Asia-Pacific region with mortality rate varying between 3% and 30%. Long-term neuropsychiatric sequelae developed in 30–50% of the survivors. There is no available antiviral therapy for JE. JE vaccines play a major role in preventing this devastating disease. The incidence of JE declined over years and the age distribution shifted toward adults in countries where JE immunization program exists. Mouse brain–JE vaccine is currently replaced by inactivated Vero cell-derived vaccine and live-attenuated vaccine using SA14-14-2 strain, and live chimeric JE vaccines. These three types of JE vaccines are associated with favorable efficacy and safety profiles. Common adverse reactions include injection site reactions and fever, and severe adverse reactions are rare.

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### Introduction

Japanese encephalitis (JE) was first described as an unusual outbreaks of summer encephalitis in Japan during the 19th century.<sup>1,2</sup> JE virus (JEV) was later isolated from a human brain in the 1930s.<sup>2</sup> Subsequently, it was recognized as an endemic disease in the Asia-Pacific region, including Japan, China, Korea, Taiwan, India, Pakistan, the Philippines, and Australia.<sup>3</sup> JE has become a notifiable disease in Taiwan since 1955. JEV is a mosquito-borne *Flavivirus* belonged to the family *Flaviviridae*. JEV can be further divided into five genotypes according to the E gene and genomic sequences.<sup>4</sup> Wading and water birds are natural hosts and carriers of JEV. Several livestock species may serve as amplifying hosts.<sup>1,3</sup> Domestic and wild pigs play the most crucial role in supplying virus in blood for infection of feeding mosquitoes.<sup>1</sup> Humans are dead-end hosts and most infected people are asymptomatic. Therefore, it is difficult to realize the accurate incidence of JE and the disease burden may be underestimated. It is estimated that less than 1% of JEV-infected humans develop disease.<sup>3</sup> Clinical manifestations range from mild disorientation or subtle personality change to confusion, delirium, and even coma. Typical thalamic lesions on computed tomography and/or magnetic resonance imaging had a sensitivity of 23% and a specificity of 100% for the diagnosis of JE.<sup>5</sup> Mortality rate varying between 3% and 30%. Long-term neuropsychiatric sequelae developed in 30% to 50% of the survivors, such as persistent motor deficit, learning difficulties, behavior problems, and personality change.<sup>4,6</sup> Several reports show that JE in young children and the elderly were more likely to be associated with severe sequelae and a higher mortality rate than young adults.<sup>6,7</sup>

### Epidemiology

According to a systematic review including 24 JE endemic countries published in 2011,<sup>8</sup> approximately 67,099 JE cases occur annually with an overall incidence of 1.8 per 1,00,000. About 50% of these cases occurred in China and near 75% were children aged 0 to 14 years old. All age groups have the risk to infect JE while most infections occurred in children in the past. However, the age distribution shifted toward adults currently in countries where JE immunization program exists.<sup>7,9–12</sup> Due to the introduction of JE vaccine, urbanization and improved sanitary and public health measures, the incidence of JE decreased year by year in many endemic countries. The estimated incidence of JE in Korea was 0.1–1.8 per 1,00,000 population during 1980–1984 and decreased to 0.013–0.055 per 1,00,000 population during 2007–2010.<sup>9</sup> In Japan, the incidence dropped from over 1,000 cases every year in the 1960s to less than 10 cases annually in the 2000s. The decline of JE was also observed in China and Taiwan during the similar period.<sup>4,10,11</sup> However, JE has not been eliminated globally. Sporadic outbreaks are still important issues in some endemic areas, such as the outbreak in northern India and Nepal in 2005.<sup>2</sup>

The first JEV isolated in 1935 belonged to genotype III that was prevalent in a broad region encompassing Japan, China, Taiwan, Vietnam, India, and Sri Lanka.<sup>13</sup> However, type III declined both in number and genetic diversity and type I has become the dominant genotype over the years.<sup>4,14</sup> Genotype I had replaced genotype III in Thailand and Vietnam after the 1980s and the 1990s, respectively.<sup>15,16</sup> A study from Japan also showed that all isolated JEVs have changed to genotype I since 1994.<sup>13</sup> National surveillance JEV data in China showed that genotype I accounted for 71% from 2001 to 2005.<sup>14</sup> Most JEV

isolated in Australia belonged to genotype II similar with Malaysian and Indonesian isolates. However, genotype I JEV was also isolated for the first time in Australia in 2000.<sup>17</sup> The switch phenomenon of genotypes is not well explained. Possible reasons might be that genotype I JEV has increased infectivity for birds and wind-blown mosquitoes or viremic migratory birds spread JEV to new territories by chance.<sup>2,16</sup>

In Taiwan, annual JE incidence rate of 1.65 to 2.04 cases per 1,00,000 people between 1966 and 1970 decreased gradually after 1971 because universal JE vaccination program for children older than 15 months was started in 1968. The average annual incidence rate of JE was approximately 0.118 cases per 1,00,000 people between 2002 and 2012.<sup>12</sup> The predominant genotype was genotype III from 2005 to 2007, and genotype I increased in incidence from 2008 to 2012.<sup>18</sup> Further seroprevalence study showed that the cohort born between 1963 and 1975, who generally received two or three doses of the mouse brain-derived JE vaccine and were administered the last booster dose more than 20 years ago, exhibited the lowest positive rate of neutralizing antibody against JE. Seroprevalence of JE was relatively higher in male and in people living in rural areas.<sup>12</sup> Although the incidence of JE declines over years, this devastating disease cannot be fully resolved. Similar to other countries with universal JE vaccination program, JE has become uncommon in children. The main age group of the confirmed JE cases in Taiwan has shifted from young children to adults over 30 years of age.<sup>12</sup>

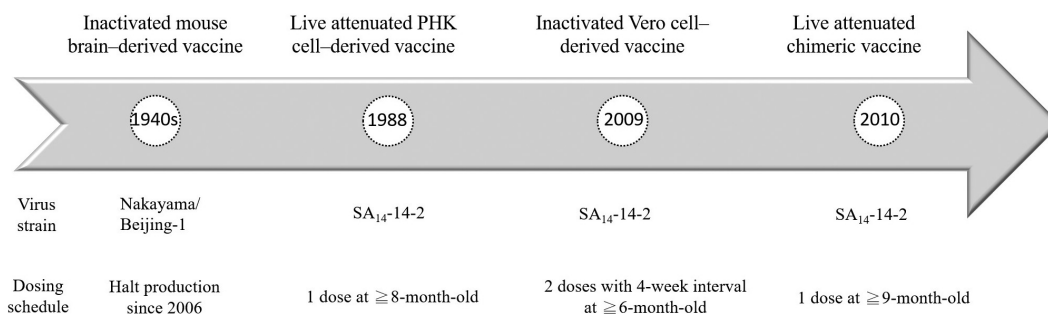
### Safety of Japanese encephalitis vaccines

According to the recommendation from the World Health Organization (WHO), JE vaccination should be integrated into national immunization schedules in all areas where JE is recognized as a public health priority.<sup>19</sup> There are four types of JE vaccines, including (1) inactivated mouse brain-derived JE vaccine, (2) primary hamster kidney (PHK) cell-derived, live-attenuated vaccine, (3) inactivated Vero cell-derived, alum-adjuvanted JE vaccine, and (4) live-attenuated chimeric JE vaccine (Figure 1). Although all current JE vaccines are derived from genotype III strains, they are found to elicit protective levels of neutralizing antibodies against heterologous strains of other genotypes.<sup>18,20,21</sup> Mouse brain-derived vaccine (MBDV) is currently replaced by inactivated Vero cell-derived vaccine and live-attenuated vaccine using SA14-14-2 strain and live chimeric JE vaccines. Overall, all the three currently available JE vaccines in the market have good efficacy and safety profiles according to published systematic review.<sup>22</sup>

### Inactivated mouse brain-derived JE vaccine

Inactivated MBDV is the first licensed JE vaccine under the trade name of JE-Vax and has been used internationally for a long time. It is produced by inoculating suckling mice intracerebrally with the virus and purifying inactivated virus suspension by ultracentrifugation.<sup>18,23</sup> Inactivated mouse brain-derived JE vaccine uses two JEV stains, that is Nakayama and Beijing-1 strain. JE vaccines containing both the strains were equally capable of eliciting high levels of serum antibody and protective efficacy against a wide range of JEV strains.<sup>23–26</sup> These two inactivated mouse brain-derived JE vaccines had been used widely in endemic countries including Japan, South Korea, Taiwan, India, Vietnam, and Thailand.<sup>23,27</sup> Inactivated MBDV containing Nakayama strain has been used in Taiwan for routine vaccination since 1968.<sup>12</sup> Inactivated MBDV had several disadvantages including higher reactogenicity than newer JE vaccines, a higher number of doses required and variability of manufacturing.<sup>18,19,23</sup> Local reactions including tenderness, swelling, and/or redness occur in around 20% of vaccinees. Systemic side effects such as headache, myalgia, fever, and gastrointestinal discomforts were reported in approximately 10% of vaccine recipients.<sup>27</sup> Post-marketing surveillance revealed a report rate of 2.8 per 1,00,000 vaccinations for total adverse events from 1996 through 1998 in Japan and 15 per 1,00,000 vaccinations during 1993 and 1998 in the United States.<sup>28</sup> Adverse events following inactivated MBDV in the United States during 1999 and 2009 was 24 per 100,000 doses distributed which consisting of 35% hypersensitivity reactions and 1% neurologic event.<sup>29</sup>

Because MBDV may contain minute amounts of basic myelin protein from mouse brain, autoimmune neurological disorder including acute disseminated encephalomyelitis (ADEM) has been a theoretical safety concern of MBDV since the development of this vaccine.<sup>27,28,30</sup> Several children diagnosed of ADEM after receiving inactivated MBDV were reported in the 1990s in Japan.<sup>31,32</sup> Notifications of neurological disorders, including ADEM, multiple sclerosis, myelitis and cognitive dysfunction, were reported in adults within one month after MBDV vaccination during 1980s and 1990s in Denmark.<sup>30,33</sup> Nevertheless, there has been no case-control study to prove or disprove such an association. WHO suggested that inactivated MBDV should be replaced by the newer generation JE vaccines based on a higher incidence of other adverse reactions associated with MBDV.<sup>19</sup> The production of MBDV was then halted in 2006 and all the remaining supplies are limited.<sup>34</sup>



**Figure 1.** Timeline of the development of four main Japanese encephalitis vaccines.

The dosing schedule is in accordance with WHO recommendation for the primary series of Japanese encephalitis vaccination. Many endemic countries also recommend a booster dose shortly after the primary series and/or entry to elementary school.

### **PHK cell-derived, live-attenuated vaccine**

A PHK cell-derived, live-attenuated vaccine based on the SA14-14-2 strain of the JEV has been used in China since 1988.<sup>18,19,23,27</sup> The SA14-14-2 virus was demonstrated to be highly attenuated for various JE susceptible animals and be excellent in safety and efficacy.<sup>23,27,35</sup> This vaccine has been widely used in some Asian countries including South Korea, Nepal, India, Cambodia, Sri Lanka, and Thailand over the past decade.<sup>2,23,27</sup> After the introduction of PHK cell-derived, live-attenuated SA14-14-2 JE vaccine into national immunization program, the JE incidence has declined considerably in China, India, and Nepal.<sup>36-39</sup> A case-control study in Nepal provided evidence that the efficacy of a single dose of live-attenuated SA14-14-2 was more than 90% and might confront clinical JE disease for at least 5 years.<sup>36,40,41</sup> Another study on immunogenicity and safety of live attenuated SA14-14-2 JE vaccine in India showed that a single dose induced protective immunity in both JE seronegative and naturally seropositive adults.<sup>42</sup> Almost 95.5% of the participants remained seroprotected at the end of 12-month follow-up.<sup>42</sup> A 30-day follow-up study of live-attenuated SA14-14-2 JE vaccine in 26,239 children showed that the incidence of encephalitis, meningitis, all-cause hospitalization or other serious adverse events was no higher than the control group.<sup>43</sup> The risk ratios of all-cause hospitalization were 0.70 (95% confidence interval 0.43–1.15), and fever was 0.79 (95% confidence interval 0.56–1.11). Live-attenuated SA14-14-2 JE was evaluated in another one-year follow-up study in 305 children. Solicited local reactions were graded as less than severe and were reported during the first three days post-vaccination mostly.<sup>44</sup> Systemic reactions were mild, including anorexia, fever, and insomnia. A total of 26 serious adverse events were recorded, and all these events were judged to be unrelated to vaccination.<sup>44</sup> According to the post-marketing surveillance in China, the reported rate of adverse events and serious adverse events following immunization in 6024 cases was 96.55 and 1.12 per million doses, respectively.<sup>45</sup> Common adverse events included local reactions such as redness (0.2–24.1%), swelling (0.4–7.9%), and pain (0.9–37.5%) at injection site. Fever (4.9–25%) was the most common systemic reaction associated with live-attenuated SA14-14-2 JE vaccine.<sup>36</sup> Several serious adverse events including death and meningoencephalitis have been reported. There was no sufficient evidence for causality based on available data.<sup>45-47</sup>

### **Inactivated, Vero cell-derived, JE vaccine**

Inactivated, Vero cell-derived, alum-adsorbed JE vaccine is produced by purification of SA14-14-2 strain virus grown in Vero cells.<sup>19</sup> This vaccine had non-inferior immunogenicity to a MBDV and was licensed under one of the three trade names, that are IXIARO, JESPECT, and JEEV, in the USA, Europe, Canada, Australia, Hong Kong, Switzerland, and India since 2009.<sup>18,19,23,27,34,48</sup> The initial licensure was limited to adults and was later approved for pediatric use in early 2013.<sup>23,34,49</sup> Vero cell-derived vaccine has high seroprotection rates ranging from 93 to 99% one month following completion of the two-dose primary series.<sup>18,19</sup> Seroprotection rate was 95.7% one month following the booster dose among children aged 1–2 years living in endemic area.<sup>18,19</sup>

In contrast to MBDV, Vero cell-derived JE vaccine reduces the potential risk of contamination from host cell proteins and nucleic acids.<sup>27,50</sup> Both pre-licensure clinical trials and post-marketing surveillance data demonstrated good safety profiles of the vaccine.<sup>51-53</sup> Yun et al. conducted a post-marketing surveillance to evaluate the safety of a Vero cell-derived JE vaccine booster dose following previous MBDV vaccination in children.<sup>51</sup> Solicited adverse events were mild with 44.7% of injection site tenderness, 26.2% of injection site erythema, and 1.1% of fever. In one study with enrollment of both adults and children in the USA, the reporting rates of adverse events and serious adverse events following immunization were 14.8 and 1.1 per 100,000 doses distributed, respectively.<sup>52</sup> A few local and systemic reactions were observed after Vero cell-derived JE vaccination in 152 Thai children. Serious adverse events were reported in 21 children and were considered to be unrelated to vaccination.<sup>53</sup> A systematic review of reports from Asia-Pacific area showed that both PHK cell-derived, live-attenuated SA<sub>14</sub>-14-2 JE vaccine and inactivated, Vero cell-derived, alum-adsorbed JE vaccine had acceptable safety without significant difference. The pooled adverse reaction rates were 18.09% and 12.49%, respectively.<sup>54</sup>

### **Live-attenuated chimeric JE vaccine**

Live-attenuated chimeric JE vaccine was created by replacing the pre-membrane (prM) and envelope (E) coding sequences of the yellow fever live-attenuated 17D vaccine virus with the analogous sequences coding for the antigenic determinants from the SA14-14-2 live-attenuated JE vaccine virus. The vaccine virus is produced in Vero cells.<sup>18,19</sup> The yellow fever 17D vaccine virus was chosen due to commendable safety and efficacy for several decades.<sup>27,55,56</sup> Live-attenuated chimeric JE vaccine is also unlikely to be transmitted by mosquitoes from vaccinated persons to other hosts.<sup>23,27,57</sup> This vaccine is designated JE-CV, ChimeriVax-JE, IMOJEV, or THAIJEV and is licensed in Australia and Thailand since 2010.<sup>23,56</sup> High seroprotection rates were reported from children from endemic countries and from adults from non-endemic countries one month after administration of a single dose of liver chimeric JE vaccine.<sup>18,19,56</sup>

In a randomized, controlled, double-blind Phase III study performed in Australia and the USA comparing the immunogenicity and safety of JE-CV and MBDV showed that JE-CV had a significant lower adverse reaction rate (67.6%) than that of MBDV (82.2%) ( $p < .001$ ). The reactogenicity profile of JE-CV was comparable with that of placebo.<sup>58</sup> According to another two comparative studies, JE-CV also have lower estimates of reactogenicity and other safety endpoints including serious adverse events, injection site reactions, and systemic reactions than live-attenuated SA14-14-2 JE vaccine.<sup>59,60</sup> Moreover, clinical studies and post-marketing surveillance all showed favorable safety profile of JE-CV (Table 1).<sup>61-68</sup> The most common adverse effects were injection site reaction with incidence of 6.3% to 37.8% and fever (3.6%–39.0%). Solicited adverse reactions following vaccination were most frequently reported in children younger than 24 months of age.<sup>63,68</sup> Few serious adverse reactions had been reported, but further investigations showed unrelatedness to JE-CV vaccination.

**Table 1.** Summary of investigations providing safety data of the live-attenuated chimeric Japanese encephalitis vaccine.

Year	Country	Participants	Number of vaccine doses	Adverse events	Serious adverse events (SAE)
2008	Thailand <sup>66</sup>	Children	300	<ul style="list-style-type: none"> <li>• No immediate reactions</li> <li>• No withdrawals for adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• No vaccine related SAE</li> </ul>
2008	Thailand	Children	1097	<ul style="list-style-type: none"> <li>• Injection site reaction 39.3%</li> <li>• Fever 20.5%</li> </ul>	<ul style="list-style-type: none"> <li>• No vaccine related SAE</li> </ul>
2010	Philippines <sup>65</sup>	Children	391	<ul style="list-style-type: none"> <li>• Injection site reaction 23.5–30.4%</li> <li>• Fever 2.2–14.2%</li> <li>• Malaise 13–14.2%</li> </ul>	<ul style="list-style-type: none"> <li>• No vaccine related SAE: 1 suspected dengue fever, 1 febrile convulsion</li> </ul>
2013–2014	South Korea <sup>64</sup>	Children	119	<ul style="list-style-type: none"> <li>• Injection site reaction 37.8%</li> <li>• Fever 12.6%</li> <li>• Malaise 40.3%</li> </ul>	<ul style="list-style-type: none"> <li>• No vaccine related SAE with a reporting rate of 3.4%</li> </ul>
2013–2015	Thailand <sup>61</sup>	Children	10000	<ul style="list-style-type: none"> <li>• Febrile convulsion 0.27%</li> </ul>	<ul style="list-style-type: none"> <li>• 3 moderate urticaria related to vaccination</li> </ul>
2015	Vietnam <sup>63</sup>	Children and adults	250	<ul style="list-style-type: none"> <li>• Injection site reactions 25.2%</li> <li>• Fever 10.4%</li> </ul>	<ul style="list-style-type: none"> <li>• No vaccine related SAE: 1 dermatitis, 1 syncope</li> </ul>
2017–2018	Taiwan <sup>62</sup>	Children	1078248	<ul style="list-style-type: none"> <li>• Fever 39%</li> <li>• Systemic rash 20%</li> <li>• Local erythema 8%</li> </ul>	<ul style="list-style-type: none"> <li>• No vaccine related SAE: 1 viral URI<sup>a</sup>, 1 cellulitis, 1 febrile seizures, 1 FSGN<sup>b</sup></li> </ul>
2015–2019	South Korea <sup>68</sup>	Children and adult	810	<ul style="list-style-type: none"> <li>• Injection site reaction 6.3%</li> <li>• Fever 3.58%</li> </ul>	<ul style="list-style-type: none"> <li>• No vaccine related SAE: 2 pneumonia, 1 cellulitis, 1 UTI<sup>c</sup></li> </ul>

<sup>a</sup>URI, upper respiratory tract infection. <sup>b</sup>FSGN, focal segmental glomerulonephritis. <sup>c</sup>UTI, urinary tract infection.

MBDV in national immunization program in Taiwan has been replaced by JE–CV since May 2017. A post-licensure safety surveillance of JE–CV was conducted in Taiwan with a total of 1,078,248 JE–CV doses distributed from May 2017 to 2018.<sup>62</sup> A total of 51 adverse events were reported from 30 vaccinees, corresponding to a reporting rate of 2.8 per 100,000 doses distributed. Adverse events occurred a median of one day after vaccination. Fever (39%), systemic rashes (20%), local redness (8%), fatigue/irritability (8%) and decreased appetite (8%) accounted for the majority. No neurological and severe hypersensitivity adverse reaction was recorded. The reporting rate of serious adverse events was 0.37 per 100,000 doses distributed, which included viral respiratory tract infection, cellulitis, focal segmental glomerulosclerosis, and febrile seizures. These serious adverse events were not considered to be attributed to the use of JE–CV.

## Conclusion

JE is believed to be an underestimated disease because most infected people are asymptomatic. The mortality rate is up to 30% and 30%–50% of survivors have neuropsychiatric sequelae. Vaccination plays the most important role in reducing the disease burden. Nowadays, inactivated MBDV was replaced by three newer JE vaccines, which had good efficacy and safety. Common adverse reactions include injection site reactions and fever, and severe adverse reactions were rare. Clinical studies and post-marketing surveillance data also proved favorable safety profile of SA14-14-2 JE vaccine and JE–CV. Continuous surveillance of the safety of JE vaccines is still imperative in the future.

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## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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